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SEARCH REQUEST FORM

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Scientific and Technical Information Center

CHEM/CHEM. (STIC)

Requester's Full Name: Jeffrey E. Russel Examiner #: 62785 Date: 9-28-2002

Art Unit: 1653 Phone Number 308-3975 Serial Number: 09/781,133

Mail Box and Bldg/Room Location: CM1-6A01/CM1-9B07 9B01 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Methods of Enhancing the Bioavailability of A Drug

Inventors (please provide full names): N. Hayward, M. Gefter

Earliest Priority Filing Date: 2-9-2001

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

Please search SEQ ID NO: 1 (LVFF) in STN in the U.S. patent application sequence database (pending and issued) and in Geneseq/Swissprot/PIR. Please require any hits to have 10 or fewer residues.

Thank you.

JER

Alzheimer
modulate?
aggregate?
amyloid
exhibit?
neurotoxic?
neuroprotect

1=4

mc

****

STAFF USE ONLY

Searcher: D. Schreiber

Searcher Phone #: 308-4292

Searcher Location: CM1 6A03

Date Searcher Picked Up: 9/30

Date Completed: 10/3

	Seq	Text
Searcher Prep & Review Time:	6	16
Clerical Prep Time:		
Online Time:	5	32

Type of Search

NA Sequence (#)	
AA Sequence (#)	2
Structure (#)	
Bibliographic	✓
Litigation	
Fulltext	
Patent Family	
Other	

Vendors and cost where applicable

STN 176.13

Dialog

Questel/Orbit

Dr.Link

Lexis/Nexis

Sequence Systems Compugen

WWW/Internet

Other (specify)

PTO-1590 (8-01)

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(FILE 'HCAPLUS' ENTERED AT 07:51:42 ON 03 OCT 2002)
L14 40 S L11 OR L13

=> d que l14
L1 4645 SEA FILE=REGISTRY LVFF/SQSP
L2 368455 SEA FILE=REGISTRY SQL<=10
L3 278 SEA FILE=REGISTRY L1 AND L2
L4 77 SEA FILE=HCAPLUS L3
L5 49 SEA FILE=HCAPLUS L4 NOT PY>2001
L6 3 SEA FILE=HCAPLUS L5 AND HIV
L7 46 SEA FILE=HCAPLUS L5 NOT L6
L8 37 SEA FILE=HCAPLUS L7 AND AMYLOID
L9 9 SEA FILE=HCAPLUS L7 NOT L8
L10 1 SEA FILE=HCAPLUS L9 AND (NEUROLOG? OR NERV?)
L11 38 SEA FILE=HCAPLUS L8 OR L10
L12 8 SEA FILE=HCAPLUS L9 NOT L10
L13 2 SEA FILE=HCAPLUS L12 AND MEMORY?
L14 40 SEA FILE=HCAPLUS L11 OR L13

=> d ibib abs l14 1-40

L14 ANSWER 1 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:146750 HCAPLUS
TITLE: Characterization of cholyl-leu-val-phe-phe-ala-OH as an inhibitor of ***amyloid*** beta-peptide polymerization
AUTHOR(S): Findeis, Mark A.; Lee, Jung-Ja; Kelley, Michael; Wakefield, James D.; Zhang, Ming-Hua; Chin, Joseph; Kubasek, William; Molineaux, Susan M.
CORPORATE SOURCE: Praecis Pharmaceuticals Incorporated, Waltham, MA, 02451-1420, USA
SOURCE: Amyloid (2001), 8(4), 231-241
CODEN: AIJIET; ISSN: 1350-6129
PUBLISHER: Parthenon Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cholyl-LVFFA-OH (PPI-368) is an org.-modified peptide based on the sequence of ***amyloid*** beta-peptide (A.beta.). It is a potent and selective inhibitor of A.beta. polymn. that blocks the formation of neurotoxic species of A.beta.. In a nucleation-dependent polymn. assay of 50 .mu.M A.beta.1-40, equimolar concns. of PPI-368 block polymn. based on

turbidity and electron microscopy. Monomeric A.beta.1-40 and A.beta.1-42 are non-toxic when incubated with neuronal cell lines, but become toxic during polymn. PPI-368 coordinately delays the onset of polymn. and the formation of neurotoxic A.beta. species for both peptides. In a polymn. extension assay seeded with pre-formed A.beta. polymer, similar inhibition and dose-dependency phenomena are obsd. with PPI-368. Radiolabeled PPI-368 is incorporated into fibrils during polymn. demonstrating binding to A.beta. peptide within a fibrillar structure. Gel-filtration studies show progressive disappearance of A.beta. monomer and concomitant appearance of sol. higher mol. wt. oligomers. In the presence of submolar concns. of PPI-368, monomeric A.beta. is still present and oligomers are not obsd. PPI-368 does not inhibit the polymn. of other amyloidogenic proteins such as transthyretin (TTR) or islet ***amyloid*** polypeptide (IAPP20-29).

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 40 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:905057 HCAPLUS

DOCUMENT NUMBER: 136:18806

TITLE: Histochemically reactive zinc in plaques of the Swedish mutant .beta.- ***amyloid*** precursor protein transgenic mice

AUTHOR(S): Lee, Joo-Yong; Inhee, Mook-Jung; Koh, Jae-Young

CORPORATE SOURCE: National Creative Research Initiative Center for the Study of CNS Zinc and Department of Neurology, University of Ulsan College of Medicine, Seoul, 138-736, S. Korea

SOURCE: Journal of Neuroscience (1999), 19(11), RC10/1-RC10/5
CODEN: JNRSDS; ISSN: 0270-6474

PUBLISHER: Society for Neuroscience

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Endogenous metals such as zinc may contribute to .beta.- ***amyloid*** (A.beta.) aggregation and hence the plaque formation. In the present study, we examd. brains of four Swedish mutant ***amyloid*** precursor protein (APP) transgenic mice at 12 mo of age for histochem. reactive zinc in the plaques. Here, we report that all the Congo red (+) mature plaques contained chelatable zinc, as demonstrated by staining with the zinc-specific fluorescent dye 6-methoxy-8-quinolyl-para-toluenesulfonamide (TSQ). On the other hand, Congo red (-) pre- ***amyloid*** A.beta. deposits were not stained with TSQ. Interestingly, although cerebellum contained similar degree of pre- ***amyloid*** A.beta. deposits as cerebral cortex, it was completely devoid of Congo red- or TSQ-stained

mature plaques. Although zinc from plaques was only slowly and partially removed by a specific zinc remover, dithizone, treatment of brain sections with heparinase-III, which degrades heparan sulfate proteoglycan (HSPG), another major constituent of plaques, greatly fastened the zinc removal with dithizone. The present study has demonstrated the presence of histochem. reactive zinc in plaques, but not pre- ***amyloid*** A.beta. deposits, of the Swedish mutant APP transgenic mice. Because pre- ***amyloid*** A.beta. deposits fail to develop into congophilic plaques in cerebellum where synaptic vesicle zinc is deficient, the synaptic zinc may be a necessary element in the plaque formation. In holding zinc inside plaques, HSPG may contribute in addn. to A.beta..
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:844942 HCAPLUS
DOCUMENT NUMBER: 136:666
TITLE: Method for design of substances that enhance ***memory*** and improve the quality of life
INVENTOR(S): Roberts, Eugene
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 30 pp., Cont. of U.S. Ser. No. 797,782, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6320024	B1	20011120	US 1999-264709	19990309

PRIORITY APPLN. INFO.: US 1997-797782 B1 19970207
AB A topog. model useful to design and synthesize ***memory*** -enhancing substances is disclosed. Administration of substances designed by this method to enhance ***memory*** in mammals, including humans, is disclosed. Such substances include peptides having the amino acid sequence Val Phe Phe.
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:790341 HCAPLUS

DOCUMENT NUMBER: 136:98653
TITLE: Identification of the molecular interaction site of ***amyloid*** .beta. peptide by using a fluorescence assay
AUTHOR(S): Watanabe, K.; Segawa, T.; Nakamura, K.; Kodaka, M.; Konakahara, T.; Okuno, H.
CORPORATE SOURCE: National Institute of Advanced Industrial Science and Technology (AIST), Ibaraki, 305-8566, Japan
SOURCE: Journal of Peptide Research (2001), 58(4), 342-346
CODEN: JPERFA; ISSN: 1397-002X
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB .beta.- ***Amyloid*** peptides (A.beta.) are the main protein components of neuritic plaques and are important in the pathogenesis of Alzheimer's disease. It is reported that A.beta. itself is not toxic; however, it becomes toxic to neuronal cells once it has aggregated into ***amyloid*** fibrils by peptide-peptide interactions. In this study, to specify the mol. mechanism of aggregation, a novel fluorescence assay was designed. For this purpose, possible partial peptides (38 types of 5-mer) were synthesized on solid-phase. The mol. interactions were examd. by a fluorescence probe possessing Lys-Leu-Val-Phe-Phe (KLVFF) as a mol. recognition site. KLVFF is known to be a min. sequence for formation of the A.beta. aggregate. A specific interaction was obsd. between labeled and immobilized KLVFF. It suggests that the aggregation of A.beta. was controlled by the recognition of KLVFF itself by hydrophobic and electrostatic interactions.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:526090 HCAPLUS
DOCUMENT NUMBER: 135:92861
TITLE: Process for the preparation of N.alpha.-2-(4-nitrophenylsulfonyl)ethoxycarbonyl amino acid fluorides
INVENTOR(S): Kim, Hack-Joo; Chweh, Weonu; Kim, Young-Cheol
PATENT ASSIGNEE(S): Hyundai Pharmaceutical Ind. Co., Ltd., S. Korea
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2001051505 A1 20010719 WO 1999-KR810 19991224

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

OTHER SOURCE(S): CASREACT 135:92861; MARPAT 135:92861

AB Title amino acid fluorides p-O2NC6H4SO2CH2CH2O2CNR1CHR2COF [R1 = H, R2 = H, iso-Pr, 2-methylpropyl, tert-butoxymethyl, benzyl, 2-(tert-butoxycarbonyl)ethyl, 4-(tert-butoxycarbamido)butyl or 4-tert-butoxybenzyl] (Nsc-amino acid fluorides) were prepd. by fluorinating Nsc-amino acids with cyanuric fluoride. Thus, 1 mmol Nsc-Val-OH in CH2Cl2 was treated with 3 mmol cyanuric fluoride and 1 mmol dry pyridine under nitrogen for 30 min to afford 82% Nsc-Val-F. The Nsc-amino acids fluorides were applied, without an activation step, to the solid-phase synthesis of peptides Leu-enkephalin, A-VI-5 peptide, and .beta.- ***amyloid*** peptide.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 40 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:442785 HCAPLUS

DOCUMENT NUMBER: 135:163793

TITLE: Inhibition of .beta.- ***Amyloid*** (40) Fibrillogenesis and Disassembly of .beta.- ***Amyloid*** (40) Fibrils by Short .beta.- ***Amyloid*** Congeners Containing N-Methyl Amino Acids at Alternate Residues

AUTHOR(S): Gordon, David J.; Sciarretta, Kimberly L.; Meredith, Stephen C.

CORPORATE SOURCE: Departments of Biochemistry and Molecular Biology Molecular Genetics and Cell Biology and Pathology, The University of Chicago, Chicago, IL, 60637, USA

SOURCE: Biochemistry (2001), 40(28), 8237-8245
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A potential goal in the prevention or therapy of Alzheimer's disease is to decrease or eliminate neuritic plaques composed of fibrillar .beta.-***amyloid*** (A.beta.). In this paper we describe N-Me amino acid contg. congeners of the hydrophobic "core domain" of A.beta. that inhibit the fibrillogenesis of full-length A.beta.. These peptides also disassemble preformed fibrils of full-length A.beta.. A key feature of the inhibitor peptides is that they contain N-Me amino acids in alternating positions of the sequence. The most potent of these inhibitors, termed A.beta.16-22m, has the sequence NH2-K(Me-L)V(Me-F)F(Me-A)E-CONH2. In contrast, a peptide, NH2-KL(Me-V)(Me-F)(Me-F)(Me-A)-E-CONH2, with N-Me amino acids in consecutive order, is not a fibrillogenesis inhibitor. Another peptide contg. alternating N-Me amino acids but based on the sequence of a different fibril-forming protein, the human prion protein, is also not an inhibitor of A.beta.40 fibrillogenesis. The nonmethylated version of the inhibitor peptide, NH2-KLVFFAE-CONH2 (A.beta.16-22), is a weak fibrillogenesis inhibitor. Perhaps contrary to expectations, the A.beta.16-22m peptide is highly sol. in aq. media, and concns. in excess of 40 mg/mL can be obtained in buffers of physiol. pH and ionic strength, compared to only 2 mg/mL for A.beta.16-22. Anal. ultracentrifugation demonstrates that A.beta.16-22m is monomeric in buffer soln. Whereas A.beta.16-22 is susceptible to cleavage by chymotrypsin, the methylated inhibitor peptide A.beta.16-22m is completely resistant to this protease. Circular dichroic spectroscopy of A.beta.16-22m indicates that this peptide is a .beta.-strand, albeit with an unusual min. at 226 nm. In summary, the inhibitor motif is that of alternating N-Me and nonmethylated amino acids in a sequence crit. for A.beta.40 fibrillogenesis. These inhibitors appear to act by binding to growth sites of A.beta. nuclei and/or fibrils and preventing the propagation of the network of hydrogen bonds that is essential for the formation of an extended .beta.-sheet fibril.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 40 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:408725 HCAPLUS

DOCUMENT NUMBER: 135:174666

TITLE: Structure-Function Relationships for Inhibitors of .beta.-***Amyloid*** Toxicity Containing the Recognition Sequence KLVFF

AUTHOR(S): Lowe, Tao L.; Strzelec, Andrea; Kiessling, Laura L.; Murphy, Regina M.

CORPORATE SOURCE: Departments of Chemical Engineering and Chemistry, University of Wisconsin, Madison, WI, 53706, USA

SOURCE: Biochemistry (2001), 40(26), 7882-7889
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB .beta.- ***Amyloid*** (A.beta.), the primary protein component of Alzheimer's plaques, is neurotoxic when aggregated into fibrils. We have devised a modular strategy for generating compds. that inhibit A.beta. toxicity. These compds. contain a recognition element, designed to bind to A.beta., linked to a disrupting element, designed to interfere with A.beta. aggregation. On the basis of this strategy, a hybrid peptide was synthesized with the sequence KLVFF (residues 16-20 of A.beta.) as the recognition element and a lysine hexamer as the disrupting element; this compd. protects cells in vitro from A.beta. toxicity [Pallitto, M. M., et al. (1999) Biochem. 38, 3570]. To det. if the length of the disrupting element could be reduced, peptides were synthesized that contained the KLVFF recognition element and a sequence of one to six lysines as disrupting elements. All compds. enhanced the rate of aggregation of A.beta., with the magnitude of the effect increasing as the no. of lysines in the disrupting element increased. The greatest level of protection against A.beta. toxicity was achieved with compds. contg. disrupting elements of three or more lysines in sequence. A peptide with an anionic disrupting element, KLVFFEEEE, had activity similar to that of KLVFFKKKK, in both cellular toxicity and biophys. assays, whereas a peptide with a neutral polar disrupting element, KLVFFSSSS, was ineffective. Protective compds. retained activity even at an inhibitor:A.beta. molar ratio of 1:100, making these some of the most effective inhibitors of A.beta. toxicity reported to date. These results provide crit. insight needed to design more potent inhibitors of A.beta. toxicity and to elucidate their mechanism of action.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 8 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:275480 HCAPLUS
DOCUMENT NUMBER: 135:190291
TITLE: Computational studies on the binding of .beta.-sheet breaker (BSB) peptides on ***amyloid*** .beta.A(1-42)
AUTHOR(S): Hetenyi, C.; Kortvelyesi, T.; Penke, B.
CORPORATE SOURCE: Department of Medical Chemistry, University of Szeged, Szeged, 6720, Hung.
SOURCE: THEOCHEM (2001), 542, 25-31
CODEN: THEODJ; ISSN: 0166-1280

PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Alzheimer's disease starts with the aggregation of .beta.- ***amyloid*** peptides overproduced in the brain. The pathognomic plaques contain 50-100 peptides in parallel and/or antiparallel .beta.-pleated sheet structure. Short peptide fragments called .beta.-sheet breaker (BSB) peptides can bind specifically to .beta.- ***amyloid*** peptides hindering the assocn. and aggregation. The 3D structures of the mol. assocs. between .beta.A6-34 and BSB peptides (Soto's LPFFD, Tjernberg's KLVFF and two new ones) were calcd. theor. by AMBER force field based docking algorithms. The calcd. structures emphasize the directing effect and pivotal role of electrostatic forces and the importance of the hydrophobic interactions of the side-chains in binding of BSB peptides to the .beta.- ***amyloid*** peptide.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:857679 HCAPLUS
DOCUMENT NUMBER: 134:264506
TITLE: Neuronal oxidative stress precedes ***amyloid*** -.beta. deposition in Down syndrome
AUTHOR(S): Nunomura, Akihiko; Perry, George; Pappolla, Miguel A.; Friedland, Robert P.; Hirai, Keisuke; Chiba, Shigeru; Smith, Mark A.
CORPORATE SOURCE: Institute of Pathology, Case Western Reserve University, Cleveland, OH, 44106, USA
SOURCE: Journal of Neuropathology and Experimental Neurology (2000), 59(11), 1011-1017
CODEN: JNENAD; ISSN: 0022-3069
PUBLISHER: American Association of Neuropathologists, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The predictable chronol. sequence of pathol. events in Down syndrome (DS) provides the opportunity to rigorously investigate the relationship between oxidative stress and ***amyloid*** -.beta. (A.beta.) deposition. In this study, we report a marked accumulation of oxidized nucleic acid, 8-hydroxyguanosine (8OHG), and oxidized protein, nitrotyrosine, in the cytoplasm of cerebral neurons in DS with the levels of nucleic acid and protein oxidn. paralleling each other. Relative d. measurements of neuronal 8OHG immunoreactivity showed that there was a significant increase ($p < 0.02$) in DS ($n = 22$, ages 0.3-65 yr) compared with age-matched controls ($n = 10$, ages 0.3-64 yr). As a function of age,

8OHG immunoreactivity increased significantly in the teens and twenties ($p < 0.04$), while A.beta. burden only increased after age 30 ($p < 0.0001$). In 9 cases of DS bearing A.beta. deposition, the extent of deposits of A.beta. ending at amino acid 42 (A.beta.42) was actually assocd. with a decrease in relative 8OHG ($r = -0.79$, $p < 0.015$) while A.beta.40 was not. These findings suggest that in brains of patients with DS, increased levels of oxidative damage occur prior to the onset of A.beta. deposition.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 10 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:628174 HCAPLUS
DOCUMENT NUMBER: 133:221242
TITLE: Modulators of beta- ***amyloid*** peptide aggregation comprising D-amino acids
INVENTOR(S): Findeis, Mark A.; Phillips, Kathryn; Olson, Gary L.; Self, Christopher
PATENT ASSIGNEE(S): Praecis Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000052048	A1	20000908	WO 2000-US5574	20000303
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1161449	A1	20011212	EP 2000-916028	20000303
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008738	A	20011226	BR 2000-8738	20000303

PRIORITY APPLN. INFO.: US 1999-122736P P 19990304
WO 2000-US5574 W 20000303

AB Compds. that modulate natural .beta. ***amyloid*** peptide aggregation

are provided. The modulators of the invention comprise a peptide, preferably based on a .beta. ***amyloid*** peptide, that is comprised entirely of D-amino acids. Preferably, the peptide comprises 3-5 D-amino acid residues and includes at least two D-amino acid residues independently selected from the group consisting of D-leucine, D-phenylalanine and D-valine. In a particularly preferred embodiment, the peptide is a retro-inverso isomer of a .beta. ***amyloid*** peptide, preferably a retro-inverso isomer of A.beta.17-21. In certain embodiments, the peptide is modified at the amino-terminus, the carboxy-terminus, or both. Preferred amino-terminal modifying groups alkyl groups. Preferred carboxy-terminal modifying groups include an amide group, an acetate group, an alkyl amide group, an aryl amide group or a hydroxy group. Pharmaceutical compns. comprising the compds. of the invention, and diagnostic and treatment methods for amyloidogenic diseases using the compds. of the invention, are also disclosed.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 11 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:96000 HCAPLUS
DOCUMENT NUMBER: 132:146648
TITLE: Peptide inhibitors of .beta.- ***amyloid*** toxicity
INVENTOR(S): Kiessling, Laura L.; Murphy, Regina M.
PATENT ASSIGNEE(S): Wisconsin Alumni Research Foundation, USA
SOURCE: U.S., 15 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6022859	A	20000208	US 1997-970833	19971114

PRIORITY APPLN. INFO.: US 1996-30840P P 19961115
AB A .beta.- ***amyloid*** inhibitor is disclosed which is of relevance to the treatment of Alzheimer's disease. In one embodiment, this inhibitor comprises a recognition element that interacts specifically with .beta.- ***amyloid*** peptide and a disrupting element that alters .beta.- ***amyloid*** aggregation. In a preferable form of the present invention, the inhibitor is a peptide.
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 12 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:773575 HCAPLUS
DOCUMENT NUMBER: 132:220716
TITLE: Aged synthetic human ***amyloid*** .beta.-peptide 1-42 and related fragments induce direct acetylcholine release from rat basal forebrain tissue slices
AUTHOR(S): Forgon, Monika; Farkas, Z.; Pakaski, Magdolna; Zarandi, Marta; Penke, B.
CORPORATE SOURCE: Alzheimer's Disease Research Centre, Albert Szent-Gyorgyi Medical University, Szeged, H-6720, Hung.
SOURCE: Acta Biologica Hungarica (1998), 49(1), 71-78
CODEN: ABHUE6; ISSN: 0236-5383
PUBLISHER: Akademiai Kiado
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The direct effects of synthetic human ***amyloid*** 1-peptide 1-42 (A.beta.1-42), scrambled A.beta.1-42 (MOD1 and MOD2), and related fragments (A.beta.31-35, A.beta.34-39, and A.beta.17-21), either freshly dissolved (non-aged) or aged for 2, 4, 12 and 24 h, were studied on acetylcholine release from rat basal forebrain tissue slices. In in vitro tissue slices, A.beta.1-42 aged for 2 h, and A.beta.31-35 and A.beta.34-39 aged for 24 h evoked acetylcholine release from the basal forebrain tissue slices in a Ca2+-dependent manner. Transmitter release was not obsd. on the use of freshly dissolved A.beta.1-42 and scrambled A.beta.1-42 (MOD1 and MOD2) and A.beta.17-21 aged for 24 h. These data support the suggestion that it is the fibrillar (aggregated) form which is effective on the axon terminals and evokes direct acetylcholine release. It is proposed that one of the roles of A.beta. in the brain is the presynaptic modulation of acetylcholine release, in this way causing first an altered Ca2+-homeostasis, then cholinergic hypoactivity, and finally the retrograde degeneration of cholinergic nerve cells.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 13 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:571804 HCAPLUS
DOCUMENT NUMBER: 131:194304
TITLE: Peptides and pharmaceutical compositions thereof for treatment of disorders or diseases associated with abnormal protein folding into ***amyloid*** or ***amyloid*** -like deposits

INVENTOR(S): Soto-Jara, Claudio; Baumann, Marc H.; Frangione, Blas
PATENT ASSIGNEE(S): New York University, USA
SOURCE: U.S., 32 pp., Cont.-in-part of U.S. Ser. No. 478,326.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5948763	A	19990907	US 1996-630645	19960410
CA 2222690	AA	19961219	CA 1996-2222690	19960606
WO 9639834	A1	19961219	WO 1996-US10220	19960606
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9661129	A1	19961230	AU 1996-61129	19960606
AU 715662	B2	20000210		
EP 843516	A1	19980527	EP 1996-918482	19960606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001519753	T2	20011023	JP 1997-502245	19960606

PRIORITY APPLN. INFO.: US 1995-478326 A2 19950607
US 1996-630645 A 19960410
WO 1996-US10220 W 19960606

AB Peptides capable of interacting with a hydrophobic structural determinant on a protein or peptide for ***amyloid*** or ***amyloid*** -like deposit formation inhibit and structurally block the abnormal folding of proteins and peptides into ***amyloid*** or ***amyloid*** -like deposits. Methods for preventing, treating or detecting disorders or diseases assocd. with ***amyloid*** -like fibril deposits, such as Alzheimer's disease and prion-related encephalopathies, are also provided.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 14 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:315400 HCAPLUS
DOCUMENT NUMBER: 131:114811
TITLE: A molecular model of Alzheimer ***amyloid*** .beta.-peptide fibril formation
AUTHOR(S): Tjernberg, Lars O.; Callaway, David J. E.; Tjernberg, Agneta; Hahne, Solveig; Lilliehook, Christina; Terenius, Lars; Thyberg, Johan; Nordstedt, Christer
CORPORATE SOURCE: Laboratory of Biochemistry and Molecular Pharmacology,

Section of Drug Dependence Research, Department of Clinical Neuroscience, Karolinska Hospital, Stockholm, S-171 76, Swed.

SOURCE: Journal of Biological Chemistry (1999), 274(18), 12619-12625
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Polymn. of the ***amyloid*** beta (A.beta.) peptide into protease-resistant fibrils is a significant step in the pathogenesis of Alzheimer's disease. It has not been possible to obtain detailed structural information about this process with conventional techniques because the peptide has limited soly. and does not form crystals. In this work, exptl. results leading to a mol. level model for fibril formation are presented. Systematically selected A.beta.-fragments contg. the A.beta.16-20 sequence, previously shown essential for A.beta.-A.beta. binding, were incubated in a physiol. buffer. Electron microscopy revealed that the shortest fibril-forming sequence was A.beta.14-23. Substitutions in this decapeptide impaired fibril formation and deletion of the decapeptide from A.beta.1-42 inhibited fibril formation completely. All studied peptides that formed fibrils also formed stable dimers and/or tetramers. Mol. modeling of A.beta.14-23 oligomers in an antiparallel .beta.-sheet conformation displayed favorable hydrophobic interactions stabilized by salt bridges between all charged residues. The authors propose that this decapeptide sequence forms the core of A.beta.-fibrils, with the hydrophobic C terminus folding over this core. The identification of this fundamental sequence and the implied mol. model could facilitate the design of potential inhibitors of amyloidogenesis.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 15 OF 40 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:278142 HCAPLUS

DOCUMENT NUMBER: 131:110884

TITLE: Modified-Peptide Inhibitors of ***Amyloid*** .beta.-Peptide Polymerization

AUTHOR(S): Findeis, Mark A.; Musso, Gary M.; Arico-Muendel, Christopher C.; Benjamin, Howard W.; Hundal, Arvind M.; Lee, Jung-Ja; Chin, Joseph; Kelley, Michael; Wakefield, James; Hayward, Neil J.; Molineaux, Susan M.

CORPORATE SOURCE: PRAECIS Pharm. Inc., Cambridge, MA, 02139-1572, USA

SOURCE: Biochemistry (1999), 38(21), 6791-6800
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cellular toxicity resulting from nucleation-dependent polymn. of ***amyloid*** .beta.-peptide (A.beta.) is considered to be a major and possibly the primary component of Alzheimer's disease (AD). Inhibition of A.beta. polymn. has thus been identified as a target for the development of therapeutic agents for the treatment of AD. The intrinsic affinity of A.beta. for itself suggested that A.beta.-specific interactions could be adapted to the development of compds. that would bind to A.beta. and prevent it from polymg. A.beta.-derived peptides of fifteen residues were found to be inhibitory of A.beta. polymn. The activity of these peptides was subsequently enhanced through modification of their amino termini with specific org. reagents. Addnl. series of compds. prepd. to probe structural requirements for activity allowed redn. of the size of the inhibitors and optimization of the A.beta.-derived peptide portion to afford a lead compd., cholyl-Leu-Val-Phe-Phe-Ala-OH (PPI-368), with potent polymn. inhibitory activity but limited biochem. stability. The corresponding all-D-amino acyl analog peptide acid (PPI-433) and amide (PPI-457) retained inhibitory activity and were both stable in monkey cerebrospinal fluid for 24 h.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 16 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:184464 HCAPLUS
DOCUMENT NUMBER: 131:17404
TITLE: Immunohistochemical localization of ***amyloid*** .beta.-protein with amino-terminal aspartate in the cerebral cortex of patients with Alzheimer's disease
AUTHOR(S): Arai, Tetsuaki; Akiyama, Haruhiko; Ikeda, Kenji; Kondo, Hiromi; Mori, Hiroshi
CORPORATE SOURCE: Department of Neuropathology, Tokyo Institute of Psychiatry, Setagaya-ku, Tokyo, 156-8585, Japan
SOURCE: Brain Research (1999), 823(1,2), 202-206
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We investigated immunohistochem. the localization of ***amyloid*** .beta.-protein (A.beta.) with amino-terminal aspartate (N1[D]) in brains of patients with Alzheimer's disease, diffuse Lewy body disease and Down's

syndrome. A monoclonal antibody, 4G8, which recognizes the middle portion of A.beta., was used as a ref. antibody to label the total A.beta. deposits. Double staining with anti-A.beta.(N1[D]) and 4G8 revealed that A.beta. deposits in the subiculum and the neocortical deep layers often lacked N1[D] immunoreactivity, indicating N-terminal truncation of A.beta. in these deposits. A.beta. deposits in the neocortical superficial layers and the presubicular parvopyramidal layer always contained A.beta. with N1[D]. Such regional as well as laminar differences in the distribution of A.beta. beginning at N1[D] suggest that some local factors influence N-terminal processing of A.beta. deposited in the brain.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 17 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:166639 HCAPLUS
DOCUMENT NUMBER: 130:209984
TITLE: Synthesis of cyclosporin A conjugates for treatment of ***neurological*** disorders
INVENTOR(S): Rich, Daniel H.; Solomon, Michael E.
PATENT ASSIGNEE(S): Wisconsin Alumni Research Foundation, USA
SOURCE: PCT Int. Appl., 129 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9910374	A1	19990304	WO 1998-US17544	19980825
AU 9892038	A1	19990316	AU 1998-92038	19980825
US 6316405	B1	20011113	US 1999-242724	19990222

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1997-57751P P 19970826
WO 1998-US17544 W 19980825
OTHER SOURCE(S): MARPAT 130:209984
AB Cyclosporin A (CsA) conjugates, cyclo(V-Abu-W-X-Val-X'-Y(Z)-D-Ala-MeLeu-

MeLeu-MeVal) [V = MeLeu(3-OH), MeLeu, MeSer, MeSer-PG, MeThr, MeThr-PG, where PG is a side-chain protecting group; W = D-N-Me amino acid or N-methylglycyl residue; X, X' = N-methylleucinyl or N-methylalanyl residue; Y = lysyl, homo-lysyl, ornithinyl, lysyl-PG, homo-lysyl-PG, or ornithinyl-PG residue; Z is a polypeptide comprising 5 or more contiguous residues of A.beta. peptide], were prepd. for the treatment of neurol. disorders. Thus, the synthesis of Ac-EKLVFF-NH2/[MeLeu(3-OH)1,D-MeAla4,6,Lys7]CsA conjugate is described.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 18 OF 40 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:148924 HCAPLUS

DOCUMENT NUMBER: 130:350690

TITLE: Fleecy ***amyloid*** deposits in the internal layers of the human entorhinal cortex are comprised of N-terminal truncated fragments of A.beta.

AUTHOR(S): Thal, Dietmar Rudolf; Sassin, Irena; Schultz, Christian; Haass, Christian; Braak, Eva; Braak, Heiko

CORPORATE SOURCE: Department of Morphology, J.W. Goethe University of Frankfurt, Frankfurt a. M., 60590, Germany

SOURCE: Journal of Neuropathology and Experimental Neurology (1999), 58(2), 210-216
CODEN: JNENAD; ISSN: 0022-3069

PUBLISHER: American Association of Neuropathologists, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The deposition of ***amyloid*** in the brain is a hallmark of Alzheimer disease (AD). ***Amyloid*** deposits consist of accumulations of .beta.- ***amyloid*** (A.beta.), which is a 39-43 amino-acid peptide cleaved from the A.beta.-protein precursor (APP). Another cleavage product of APP is the P3-peptide, which consists of the amino acids 17-42 of the A.beta.-peptide. To study the deposition of N-terminal truncated forms of A.beta. in the human entorhinal cortex, serial sections from 16 autopsy cases with AD-related pathol. were immunostained with antibodies against A.beta.1-40, A.beta.1-42, A.beta.17-23, and A.beta.8-17, as well as with the Campbell-Switzer silver impregnation for ***amyloid*** . In the external entorhinal layers (pre-.beta. and pre-.gamma.), sharply delineated diffuse plaques were seen. They were labeled by silver impregnation and by all A.beta.-antibodies used. By comparison, in the internal layers (pri-.alpha., pri-.beta., and pri-.gamma.) blurred, ill-defined clouds of ***amyloid*** existed, in addn. to sharply delineated diffuse plaques. These clouds of ***amyloid*** were termed "fleecy ***amyloid*** .".

Immunohistochem., fleecy ***amyloid*** was stained by A.beta.17-23 and A.beta.1-42 antibodies, but not with antibodies against A.beta.8-17 and A.beta.1-40. Using the Campbell-Switzer technique, the fleecy ***amyloid*** deposits were fine argyrophilic ***amyloid*** fibrils. Thus, the internal entorhinal layers are susceptible to a distinct type of ***amyloid*** , namely fleecy ***amyloid*** . This fleecy ***amyloid*** obviously corresponds to N-terminal fragments of A.beta.1-42, probably representing the P3-peptide. These N-terminal truncated fragments of A.beta. are capable of creating fine fibrillar " ***amyloid*** .".

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 19 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:148185 HCAPLUS
DOCUMENT NUMBER: 130:347290
TITLE: Recognition sequence design for peptidyl modulators of .beta.- ***amyloid*** aggregation and toxicity
AUTHOR(S): Pallitto, Monica M.; Ghanta, Jyothi; Heinzelman, Peter; Kiessling, Laura L.; Murphy, Regina M.
CORPORATE SOURCE: Departments of Chemical Engineering and Chemistry, University of Wisconsin, Madison, WI, 53706, USA
SOURCE: Biochemistry (1999), 38(12), 3570-3578
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB .beta.- ***Amyloid*** (A.beta.), the primary protein component of Alzheimer's plaques, is neurotoxic when aggregated into fibrils. We have devised a modular strategy for generating compds. that inhibit A.beta. toxicity, based on linking a recognition element for A.beta. to a disrupting element designed to interfere with A.beta. aggregation. One such compd., with the 15-25 sequence of A.beta. as the recognition element and a lysine hexamer as the disrupting element, altered A.beta. aggregation kinetics and protected cells from A.beta. toxicity [Ghanta et al. (1996) J. Biol. Chem. 271, 29525]. To optimize the recognition element, peptides of 4-8 residues composed of overlapping sequences within the 15-25 domain were synthesized, along with hybrid compds. contg. those recognition sequences coupled to a lysine hexamer. None of the recognition peptides altered A.beta. aggregation kinetics and only two, KLVFF and KLVF, had any protective effect against A.beta. toxicity. The hybrid peptide KLVFF-KKKKKK dramatically altered A.beta. aggregation kinetics and aggregate morphol. and provided significantly improved protection against A.beta. toxicity compared to the recognition peptide

alone. In contrast, FAEDVG-KKKKKK possessed only modest inhibitory activity and had no marked effect on A.beta. aggregation. The scrambled sequence VLFKF was nearly as effective a recognition domain as KLVFF, suggesting the hydrophobic characteristics of the recognition sequence are crit. None of the cytoprotective peptides prevented A.beta. aggregation; rather, they increased aggregate size and altered aggregate morphol. These results suggest that coupling recognition with disrupting elements is an effective generalizable strategy for the creation of A.beta. inhibitors. Significantly, prevention of A.beta. aggregation may not be required for prevention of toxicity.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 20 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:21679 HCAPLUS
DOCUMENT NUMBER: 130:95847
TITLE: Preparation of ***amyloid*** .beta. peptides and derivatives that modulate .beta.- ***amyloid*** aggregation
INVENTOR(S): Findeis, Mark A.; Benjamin, Howard; Garnick, Marc B.; Gefter, Malcolm L.; Hundal, Arvind; Kasman, Laura; Musso, Gary; Signer, Ethan R.; Wakefield, James; Reed, Michael; Molineaux, Susan; Kubasek, William; Chin, Joseph; Lee, Jung-Ja; Kelley, Michael
PATENT ASSIGNEE(S): Praecis Pharmaceuticals, Inc., USA
SOURCE: U.S., 52 pp., Cont.-in-part of U.S. Ser. No. 404,831.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5854204	A	19981229	US 1996-612785	19960314
US 5817626	A	19981006	US 1995-404831	19950314
US 5854215	A	19981229	US 1995-475579	19950607

PRIORITY APPLN. INFO.: US 1995-404831 A2 19950314
US 1995-475579 A2 19950607
US 1995-548998 A2 19951027

AB Compds. that modulate the aggregation of amyloidogenic proteins or peptides are disclosed. The modulators of the invention can promote ***amyloid*** aggregation or, more preferably, can inhibit natural ***amyloid*** aggregation. In a preferred embodiment, the compds.

modulate the aggregation of natural .beta. ***amyloid*** peptides (.beta.-AP). In a preferred embodiment, the .beta. ***amyloid*** modulator compds. of the invention are comprised of an A.beta. aggregation core domain and a modifying group coupled thereto such that the compd. alters the aggregation or inhibits the neurotoxicity of natural .beta. ***amyloid*** peptides when contacted with the peptides. Furthermore, the modulators are capable of altering natural .beta.-AP aggregation when the natural .beta.-APs are in a molar excess amt. relative to the modulators. Pharmaceutical compns. comprising the compds. of the invention, and diagnostic and treatment methods for amyloidogenic diseases using the compds. of the invention, are also disclosed.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 21 OF 40 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:725680 HCAPLUS

DOCUMENT NUMBER: 130:91806

TITLE: Residual structure in the Alzheimer's disease peptide: probing the origin of a central hydrophobic cluster

AUTHOR(S): Zhang, Shengsheng; Casey, Nicole; Lee, Jonathan P.

CORPORATE SOURCE: Department of Chemistry, Boston University, Boston, MA, 02215, USA

SOURCE: Folding & Design (1998), 3(5), 413-422
CODEN: FODEFH; ISSN: 1359-0278

PUBLISHER: Current Biology Publications

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Structure-function studies on the Alzheimer's disease peptide show that a central hydrophobic cluster - A.beta.(17-21), LVFFA - is a prominent structural feature linked to plaque competence. The origin and stability of this cluster was probed in a 17-residue fragment which includes flanking residues that potentially help stabilize the cluster. After residue substitution, the measurement of pKas, amide exchange rates and other NMR data show that any coulombic interactions between His 14 and Glu22 are not required for the stability of the central hydrophobic cluster. In contrast, a single substitution within the cluster disrupts its integrity and causes the largest pKa shift for flanking residues, while increasing the solvent accessibility of the backbone. The integrity of the structurally dominant cluster relies primarily upon local hydrophobic interactions, rather than on interactions between the sidechains of charged flanking residues. Moreover, the conformational disposition of the cluster affects the pKas of flanking residues, underscoring its structural dominance.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR

THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 22 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:351795 HCAPLUS
DOCUMENT NUMBER: 129:38409
TITLE: Optical diagnostic agents for diagnosis of neurodegenerative diseases by means of near infra-red radiation (NIR radiation)
INVENTOR(S): Turner, Jonathan; Dyrks, Thomas; Semmler, Wolfhard; Licha, Kai; Riefke, Bjorn
PATENT ASSIGNEE(S): Institut fur Diagnostikforschung G.m.b.H. an der Freien Universitat Berlin, Germany; Turner, Jonathan; Dyrks, Thomas; Semmler, Wolfhard; Licha, Kai; Riefke, Bjorn
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9822146	A2	19980528	WO 1997-DE2559	19971029
WO 9822146	A3	19981015		
W: AU, CA, CN, HU, JP, KR, NO, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19649971	A1	19980528	DE 1996-19649971	19961119
AU 9872985	A1	19980610	AU 1998-72985	19971029
EP 942756	A2	19990922	EP 1997-948710	19971029
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1237911	A	19991208	CN 1997-199895	19971029
JP 2001506591	T2	20010522	JP 1998-523059	19971029
US 6329531	B1	20011211	US 1999-308177	19991118

PRIORITY APPLN. INFO.: DE 1996-19649971 A 19961119
WO 1997-DE2559 W 19971029
OTHER SOURCE(S): MARPAT 129:38409
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE

PRINT *

AB The invention concerns compds. Fm(-A1) (-Bn) (-WO) (I) wherein F is a dye label mol. with an absorption max. 600-1200 nm; A is a .beta.-***amyloid*** plaque binding biomol.; B is a .beta.-***amyloid*** plaque binding dye; and W is a .beta.-***amyloid*** plaque binding hydrophilic low-mol. structural element. The nos. in the formula are m = 1,2 or if n and o = 0 than m = 3-20; l and n are independently 0,1,2; o = 0,1,2,3,4 if l+n+o .gtoreq. 0. Part F in I is a cyano, squarilium, croconium, merocyano or oxonol dye with the structures II, III, IV and V (R1-R4 and R7-R10 are H, F, Cl, Br, I, nitro or -COOE1, -COOE1E2, -NHCOE1, -NHCONHE1, -NE1E2,- OE1, -OSO3OE1, -SO3OE1, -SO2NHE, -E1; E1 and E2 are independently H, satd., unsatd., linear, branched C1-C50 alkyl; the chain can include C5 or C6 arom. or cyclic condensed rings, 0-15 O atoms, 0-3 carbonyl groups or 0-5 hydroxy groups; R1-R4 and/or R7-R10 can be coupled via a six member arom. ring or they can be coupled to A, B or W; R5 and R6 are -E1, C1-C4 sulfoalkyl, alkylene, cycloalkylene chains; R11 and R12 are Ph rings with 1-3 substituents of hydroxy, carboxy, sulfate, sulfonate, alkyl, alkoxy, or carboxylic acid). The .beta.-***amyloid*** plaque binding biomol. A in I is one of the following: antibody, antibody fragment, specific peptide, protein, receptor, enzyme, enzyme substrate, nucleotide, RNA, DNA, lipoprotein, carbohydrate, saccharide, saccharide deriv., or dextran. The .beta.-***amyloid*** plaque binding dye B in I is a diazo-biphenyl compd. The structural element W in I is from the group of the following: -OSO3H, -SO3H, linear, branched, satd., unsatd., cyclic, polycyclic alkyl, alkenyl, polyalkenyl, alkynyl, aryl, alkylaryl or arylalkyl up to 60 carbon atoms, with substituents hydroxy, carboxy, sulfate, sulfonate. Coupling of part F with A, B and/or W can be via ester, ether, sec., tert., amino group, amido, ureylene, thiol, etc. groups. The invention also includes the physiol. compatible salts of the above compds. These compds. are used as contrast agents for in vivo and in vitro diagnosis of neurodegenerative diseases such as Alzheimer's disease in combination with near infra-red radiation (NIR radiation) and detection of the fluorescent or transmitted light. Further the invention concerns a test kit, consisting of at least one of the I compds., the carrier, e.g. nitrocellulose membrane, reagents and solvents. Diagnostic agents contg. said components are also disclosed.

L14 ANSWER 23 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:258273 HCAPLUS
DOCUMENT NUMBER: 129:53004
TITLE: GM1 ganglioside-bound ***amyloid*** .beta.-protein in Alzheimer's disease brain
AUTHOR(S): Yanagisawa, K.; Ihara, Y.
CORPORATE SOURCE: Department of Dementia Research, National Institute

for Longevity Sciences, Obu, 474, Japan
SOURCE: Neurobiology of Aging (1998), 19(Suppl. 1, Proceedings of the 11th Annual Tokyo Institute of Psychiatry International Symposium, 1997), S65-S67
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The central question related to .beta.-amyloidogenesis is how ***amyloid*** .beta.-protein (A.beta.) is generated and deposited. To address this issue, we investigated the early stage of .beta.-amyloidogenesis using cerebral cortices from Alzheimer's disease and Down's syndrome patients and normal aged individuals with BC05, a specific monoclonal antibody for A.beta.42, which is believed to be an initially deposited A.beta. species, as a probe. In that study, we found that A.beta.42 is bound to membranes in brains with abundant diffuse plaques, and that the bound lipid is likely GM1 ganglioside. To further characterize this novel A.beta. species, we investigated its reactivity to cholera toxin, and performed immunopptn. expts. using several anti-A.beta. monoclonal antibodies. The immunoppts. obtained with BAN052 (specific for the N-terminus of A.beta.), but not BC05 and 4G8 (specific for A.beta.17-24), showed significant A.beta. immunoreactivity and cholera toxin reactivity. The present results strongly suggest that A.beta. binds to a GM1 ganglioside in such a way that the bound A.beta. is only recognized by BAN052, of the monoclonal antibodies used in this study.

L14 ANSWER 24 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:163613 HCAPLUS
DOCUMENT NUMBER: 128:217639
TITLE: Preparation of D-amino acid peptides as modulators of .beta.- ***amyloid*** peptide aggregation
INVENTOR(S): Findeis, Mark A.; Gefter, Malcolm L.; Musso, Gary; Signer, Ethan R.; Wakefield, James; Molineaux, Susan; Chin, Joseph; Lee, Jung-Ja; Kelley, Michael; Komar-Panicucci, Sonja; Arico-Muendel, Christopher C.; Phillips, Kathryn; Hayward, Neil J.
PATENT ASSIGNEE(S): Praecis Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9808868	A1	19980305	WO 1997-US15166	19970827
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 6303567	B1	20011016	US 1996-703675	19960827
AU 9742387	A1	19980319	AU 1997-42387	19970827
AU 741199	B2	20011122		
EP 929574	A1	19990721	EP 1997-940663	19970827
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001500852	T2	20010123	JP 1998-511914	19970827

PRIORITY APPLN. INFO.: US 1996-703675 A 19960827
US 1997-897342 A 19970721
US 1995-404831 A2 19950314
US 1995-475579 A2 19950607
US 1995-548998 B2 19951027
US 1996-616081 B2 19960314
WO 1997-US15166 W 19970827

OTHER SOURCE(S): MARPAT 128:217639

AB Compds. that modulate natural .beta.- ***amyloid*** peptide aggregation are provided. The modulators of the invention comprise a peptide, preferably based on a .beta.- ***amyloid*** peptide, that is comprised entirely of D-amino acids. Preferably, the peptide comprises 3-5 D-amino acid residues and includes at least two D-amino acid residues independently selected from the group consisting of D-Leu, D-Phe, and D-Val. In a particularly preferred embodiment, the peptide is a retro-inverso isomer of a .beta.- ***amyloid*** peptide, preferably a retro-inverso isomer of A.beta.17-21. In certain embodiments, the peptide is modified at the amino-terminus, the carboxy-terminus, or both. Preferred amino-terminal modifying groups include cyclic, heterocyclic, polycyclic and branched alkyl groups. Preferred carboxy-terminal modifying groups include an amide group, an alkylamide group, an arylamide group or a hydroxy group. Pharmaceutical compns. comprising the compds. of the invention, and diagnostic and treatment methods for amyloidogenic diseases using the compds. of the invention, are also disclosed. Thus, peptide H-D-Leu-D-Val-D-Phe-D-Phe-D-Ala-NH2, prepd. by std. solid-phase methods, inhibited aggregation of natural .beta.- ***amyloid*** peptide with a change in lag time of 3.5 at a concn. of 3 .mu.M.

L14 ANSWER 25 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:137096 HCAPLUS
DOCUMENT NUMBER: 128:305262
TITLE: Measurement of peptide aggregation with pulsed-field gradient nuclear magnetic resonance spectroscopy
AUTHOR(S): Mansfield, Shawn L.; Jayawickrama, Dimuthu A.; Timmons, Jeffery S.; Larive, Cynthia K.
CORPORATE SOURCE: Department of Chemistry, University of Kansas, Lawrence, KS, 66045, USA
SOURCE: Biochimica et Biophysica Acta (1998), 1382(2), 257-265
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Interactions between hydrophobic patches in proteins are often a driving force for denaturation and aggregation. The aggregation of the .beta.-***amyloid*** peptide fragment, VHHQKLVFFAEDVGSNK (.beta.(12-28)), has been investigated in aq. soln. at low pH. This peptide contains a central hydrophobic patch spanning residues 17-21. Diffusion coeffs. measured with pulsed-field gradient NMR as a function of peptide soln. concn. were used to assess the extent of aggregation. Following the hypothesis that hydrophobic interactions are an important driving force in the aggregation of this peptide at low pH, a non-aggregating analog of the .beta.(12-28) peptide, [Gly19,20].beta.(12-28) was synthesized. In the [Gly19,20].beta.(12-28) peptide, the replacement of the two phenylalanine residues disrupts the hydrophobic interactions which drive the aggregation of .beta.(12-28). The diffusion coeff. of the [Gly19,20].beta.(12-28) peptide is invariant over the concn. range studied and provides a good est. of the monomeric diffusion coeff. of .beta.(12-28). A second peptide analog was synthesized in which the phenylalanine at position 20 was replaced with a cysteine residue. The disulfide-linked dimer, ([Cys20].beta.(12-28))2, was formed upon air oxidn. of this peptide. The diffusion coeff. of the ([Cys20].beta.(12-28))2 peptide was measured and used to est. the diffusion coeff. of the .beta.(12-28) dimer. Using the monomeric and dimeric diffusion coeffs. measured for the glycine and cysteine analogs, the concn. dependence of the .beta.(12-28) diffusion coeff. was found to be consistent with a monomer-dimer aggregation model.

L14 ANSWER 26 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:458252 HCAPLUS
DOCUMENT NUMBER: 127:107496
TITLE: Controlling ***amyloid*** .beta.-peptide fibril formation with protease-stable ligands. [Erratum to document cited in CA127:32334]
AUTHOR(S): Tjernberg, Lars O.; Lilliehook, Christina; Callaway,

David J. E.; Naslund, Jan; Hahne, Solveig; Thyberg, Johan; Terenius, Lars; Nordstedt, Christer

CORPORATE SOURCE: Lab. Biochem. Mol. Pharmacol., Sect. Drug Dependence Res., Dep. Clinical Neurosci., Karolinska Hosp., Stockholm, S-171 76, Swed.

SOURCE: Journal of Biological Chemistry (1997), 272(28), 17894
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The micrograph in Fig. 5 did not reproduce adequately. Fig. 5 is reproduced in better quality.

L14 ANSWER 27 OF 40 HCAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1997:454206 HCAPLUS

DOCUMENT NUMBER: 127:174847

TITLE: Apolipoprotein E forms stable complexes with recombinant Alzheimer's disease .beta.- ***amyloid*** precursor protein

AUTHOR(S): Haas, Cristina; Cazorla, Pilar; De Miguel, Carlos; Valdivieso, Fernando; Vazquez, Jesus

CORPORATE SOURCE: Centro de Biologia Moleuclar 'Severo Ochoa', Universidad Autonoma de Madrid, Madrid, 28049, Spain

SOURCE: Biochemical Journal (1997), 325(1), 169-175
CODEN: BIJOAK; ISSN: 0264-6021

PUBLISHER: Portland Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Apolipoprotein E (apoE), a protein genetically linked to the incidence of Alzheimer's disease, forms SDS-stable complexes in vitro with .beta.- ***amyloid*** peptide (A.beta.), the primary component of senile plaques. In the present study, the authors investigated whether apoE was able to bind full-length A.beta. precursor protein (APP). Using a maltose-binding-protein-APP fusion protein and human very-low-d. lipoprotein (VLDL), the authors detected an interaction of apoE with APP that was inhibited by A.beta. or anti-apoE antibody. Satn.-binding expts. indicated a single binding equil. with an apparent 1:1 stoichiometry and a dissocn. const. of 15 nM. An interaction was also obsd. using apoE from cerebrospinal fluid or delipidated VLDL, as well as recombinant apoE. APP.cntdot.apoE complexes were SDS-stable, and their formation was not inhibited by reducing conditions; however, they were dissocd. by SDS under reducing conditions. ApoE.cntdot.APP complexes formed high-mol.-mass aggregates, and competition expts. suggested that amino acids 14-23 of A.beta. are responsible for complex-formation. Finally, no differences

were found when studying the interaction of APP with apoE3 or apoE4. Thus, apoE may form stable complexes with the A.beta. moiety of APP with characteristics similar to those of complexes formed with isolated A.beta., and apoE-APP interactions may be pathol. relevant in vivo.

L14 ANSWER 28 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:318416 HCAPLUS
DOCUMENT NUMBER: 127:32334
TITLE: Controlling ***amyloid*** .beta.-peptide fibril formation with protease-stable ligands
AUTHOR(S): Tjernberg, Lars O.; Lilliehook, Christina; Callawya, David J. E.; Naslund, Jan; Hahne, Solveig; Thyberg, Johan; Terenius, Lars; Nordstedt, Christer
CORPORATE SOURCE: Lab. Biochem. Mol. Pharmacol., Sect. Drug Dependence Res., Dep. Clinical Neurosci., Karolinska Hosp., Stockholm, S-171 76, Swed.
SOURCE: Journal of Biological Chemistry (1997), 272(19), 12601-12605
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have previously shown that short peptides incorporating the sequence KLVFF can bind to the ~40-amino acid residue Alzheimer ***amyloid*** .beta.-peptide (A.beta.) and disrupt ***amyloid*** fibril formation. Here, it is shown that KLVFF binds stereospecifically to the homologous sequence in A.beta. (i.e. A.beta.16-20). Mol. modeling suggests that assocn. of the two homologous sequences leads to the formation of an atypical anti-parallel .beta.-sheet structure stabilized primarily by interaction between the Lys, Leu, and C-terminal Phe. By screening combinatorial pentapeptide libraries exclusively composed of D-amino acids, several ligands with a general motif contg. phenylalanine in the second position and leucine in the third position were identified. Ligands composed of D-amino acids were not only capable of binding A.beta. but also prevented formation of ***amyloid*** -like fibrils. These ligands are protease-resistant and may thus be useful as exptl. agents against ***amyloid*** fibril formation in vivo.

L14 ANSWER 29 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:134852 HCAPLUS
DOCUMENT NUMBER: 126:139860
TITLE: Peptides and pharmaceutical compositions thereof for treatment of disorders or diseases associated with abnormal protein folding into ***amyloid*** or

amyloid -like deposits
INVENTOR(S): Soto-Jara, Claudio; Baumann, Marc H.; Frangione, Blas
PATENT ASSIGNEE(S): New York University, USA
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9639834	A1	19961219	WO 1996-US10220	19960606
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5948763	A	19990907	US 1996-630645	19960410
AU 9661129	A1	19961230	AU 1996-61129	19960606
AU 715662	B2	20000210		
EP 843516	A1	19980527	EP 1996-918482	19960606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001519753	T2	20011023	JP 1997-502245	19960606

PRIORITY APPLN. INFO.: US 1995-478326 A 19950607
US 1996-630645 A 19960410
WO 1996-US10220 W 19960606

AB Novel peptides capable of interacting with a hydrophobic structural determinant on a protein or peptide for ***amyloid*** or ***amyloid*** -like deposit formation inhibit and structurally block the abnormal folding of proteins and peptides into ***amyloid*** or ***amyloid*** -like deposits are described. Methods for preventing, treating or detecting disorders or diseases assocd. with ***amyloid*** -like fibril deposits, such as Alzheimer's disease and prion-related encephalopathies, are also provided.

L14 ANSWER 30 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:716502 HCAPLUS
DOCUMENT NUMBER: 126:42544
TITLE: A strategy for designing inhibitors of .beta.-***amyloid*** toxicity
AUTHOR(S): Ghanta, Jyothi; Shen, Chih-Lung; Kiessling, Laura L.; Murphy, Regina M.
CORPORATE SOURCE: Department Chemistry, University Wisconsin, Madison, WI, 53706, USA
SOURCE: Journal of Biological Chemistry (1996), 271(47), 29525-29528

CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB .beta.- ***Amyloid*** peptide is the major protein component of Alzheimer's plaques. When aggregated into ***amyloid*** fibrils, the peptide is toxic to neuronal cells. Here, an approach to the design of inhibitors of .beta.- ***amyloid*** toxicity is described; in this strategy, a recognition element, which interacts specifically with .beta.- ***amyloid*** , is combined with a disrupting element, which alters .beta.- ***amyloid*** aggregation pathways. The synthesis, biophys. characterization, and biol. activity of such an inhibitor is reported. This prototype inhibitor is composed of residues 15-25 of .beta.- ***amyloid*** peptide, designed to function as the recognition element, linked to an oligolysine disrupting element. The inhibitor does not alter the apparent secondary structure of .beta.- ***amyloid*** nor prevent its aggregation; rather, it causes changes in aggregation kinetics and higher order structural characteristics of the aggregate. Evidence for these effects includes changes in fibril morphol. and a redn. in thioflavin T fluorescence. In addn. to its influence on the phys. properties of .beta.- ***amyloid*** aggregates, the inhibitor completely blocks .beta.- ***amyloid*** toxicity to PC-12 cells. Together, these data suggest that this general strategy for design of .beta.- ***amyloid*** toxicity inhibitors is effective. Significantly, these results demonstrate that complete disruption of ***amyloid*** fibril formation is not necessary for abrogation of toxicity.

L14 ANSWER 31 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:592336 HCAPLUS
DOCUMENT NUMBER: 125:292787
TITLE: Inhibition of Alzheimer's amyloidosis by peptides that prevent .beta.-sheet conformation
AUTHOR(S): Soto, Claudio; Kindy, Mark S.; Baumann, Marc; Frangione, Blas
CORPORATE SOURCE: Dep. Neurology, Dep. Pathology, New York Univ. Med. Center, New York, NY, 10016, USA
SOURCE: Biochemical and Biophysical Research Communications (1996), 226(3), 672-680
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB ***Amyloid*** .beta.-peptide (A.beta.) is a major fibrillar component of neuritic plaques in Alzheimer's disease (AD) brains and is related to

the pathogenesis of the disease. We hypothesized that ***amyloid*** formation could be inhibited by peptides homologous to A.beta. (position 17-21) with a similar degree of hydrophobicity, but with a very low propensity to adopt a .beta.-sheet conformation by incorporating proline residues (anti-.beta.-sheet peptides or .beta.-sheet inhibitors). An 11-residue peptide with these characteristics binds to A.beta., inhibits A.beta. fibril formation, and partially disaggregates preformed fibrils in vitro. Shorter anti-.beta.-sheet peptides and analogs contg. D-amino acids are also able to inhibit A.beta. fibrillogenesis. The latter are more resistant to proteolytic degrdn. and may serve as a starting point ot design more efficient peptides derivs. to inhibit amyloidogenesis in vivo.

L14 ANSWER 32 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:233397 HCAPLUS
DOCUMENT NUMBER: 124:306542
TITLE: Arrest of .beta.- ***amyloid*** fibril formation by a pentapeptide ligand
AUTHOR(S): Tjernberg, Lars O.; Naeslund, Jan; Lindqvist, Fredrik; Johansson, Jan; Karlstroem, Anders R.; Thyberg, Johan; Terenius, Lars; Nordstedt, Christer
CORPORATE SOURCE: Laboratory Biochemistry Molecular Pharmacology, Karolinska Hospital, Stockholm, S-171 76, Swed.
SOURCE: Journal of Biological Chemistry (1996), 271(15), 8545-8
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Polymn. of ***amyloid*** .beta.-peptide (A.beta.) into ***amyloid*** fibrils is a crit. step in the pathogenesis of Alzheimer's disease. Here, we show that peptides incorporating a short A.beta. fragment (KLVFF; A.beta.16-20) can bind full-length A.beta. and prevent its assembly into ***amyloid*** fibrils. Through alanine substitution, it was demonstrated that amino acids Lys16, Leu17, and Phe20 are crit. for binding to A.beta. and inhibition of A.beta. fibril formation. A mutant A.beta. mol., in which these residues had been substituted, had a markedly reduced capability of forming ***amyloid*** fibrils. The present data suggest that residues A.beta.16-20 serve as a binding sequence during A.beta. polymn. and fibril formation. Moreover, the present KLVFF peptide may serve as a lead compd. for the development of peptide and nonpeptide agents aimed at inhibiting A.beta. amyloidogenesis in vivo.

L14 ANSWER 33 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:594478 HCAPLUS

DOCUMENT NUMBER: 123:977
TITLE: Peptides for amelioration of amnesia in Alzheimer's disease caused by deposition of ***amyloid*** beta protein
INVENTOR(S): Roberts, Eugene
PATENT ASSIGNEE(S): City of Hope, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9508999	A1	19950406	WO 1994-US10475	19940916
W: CA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5470951	A	19951128	US 1993-127904	19930929
EP 670731	A1	19950913	EP 1994-929818	19940916
R: DE, FR, GB				

PRIORITY APPLN. INFO.: US 1993-127904 19930929
WO 1994-US10475 19940916
OTHER SOURCE(S): MARPAT 123:977
AB Three non-amnestic and non-memory enhancing peptides, Asp-Phe-Phe-Val-Gly, Gln-Phe-Val-Gly, and Ala-Ile-Phe-Thr, that block the amnestic effects of .beta.-(12-28), a peptide homologs to ***amyloid*** .beta. protein (A.beta.), are disclosed. The invention relates to amelioration of amnesia and other neurotoxicity in Alzheimer's disease (AD) caused by deposition of A.beta. and, therefore, relates to attenuation of the disease process and consequential improvement of the quality of life for the individuals suffering from AD. The effects of a series of peptides on the amnestic effects of .beta.(12-28) in mice were detd.

L14 ANSWER 34 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:573971 HCAPLUS
DOCUMENT NUMBER: 122:306561
TITLE: Use of a topographic receptor model to identify the binding site for amnestic peptides and the design of ***memory*** -enhancing drugs
INVENTOR(S): Roberts, Eugene
PATENT ASSIGNEE(S): City of Hope, USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9507093	A1	19950316	WO 1994-US10083	19940908
W: CA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5652334	A	19970729	US 1993-117927	19930908
CA 2148452	AA	19950315	CA 1994-2148452	19940908
EP 668776	A1	19950830	EP 1994-928038	19940908
EP 668776	B1	20000412		
R: DE, FR, GB				

PRIORITY APPLN. INFO.: US 1993-117927 19930908
WO 1994-US10083 19940908

AB A topog. model useful to design and synthesize ***memory*** -enhancing substances is disclosed. Administration of substances designed by this method to enhance ***memory*** in mammals, including humans, is disclosed. Such substances include peptides having the amino acid sequence Val-Phe-Phe. Compds. with potential uses as ***memory*** enhancers were tested by their effects on learning an avoidance response. The structure and activity relationships were used to det. the topog. for the binding sites for these compds. A potential ***memory*** -enhancing substance is designed on the basis of these data.

L14 ANSWER 35 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:495517 HCAPLUS
DOCUMENT NUMBER: 123:4989
TITLE: Location of an epitope shared by Alzheimer's ***amyloid*** peptide and brain creatine kinase using a newly developed monoclonal antibody
AUTHOR(S): Cazorla, Pilar; Aldudo, Jesus; Haas, Cristina; Vazquez, Jesus; Valdivieso, Fernando; Bullido, Maria J.
CORPORATE SOURCE: Centro de Biologia Molecular Severo Ochoa (CSIC-UAM), Universidad Autonoma de Madrid, Madrid, 28049, Spain
SOURCE: Biochimica et Biophysica Acta (1995), 1270(2-3), 149-56
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB ***Amyloid*** plaques, composed mainly by a peptide termed A4-***amyloid*** , derived by proteolytic processing from the

amyloid precursor protein (APP), are a hallmark in the brain of Alzheimer's disease patients. The authors have prepd. a collection of monoclonal antibodies as tools to study APP expression and proteolysis in different systems. One of these, 5AH10, raised against residues 9-22 of A4-peptide, was selected for its ability to recognize only A4 subpeptides having the intact APP-secretase target sequence, as well as whole recombinant APP. By using synthetic subpeptides, the authors have located 5AH10 epitope between amino acids 15 and 22 of A4. In addn., 5AH10 showed a strong immunoreactivity to a 47-kDa protein present in rat brain exts., that was identified as the B (brain-specific) subunit of creatine kinase by immunochem. data and direct N-terminal sequencing. The cross-reaction obsd. is most probably due to a high degree of sequence identity between amino acids 15 to 22 of A4 peptide and amino acids 9 to 16 of rat B creatine kinase. 5AH10 did not recognize the muscle-specific isoform (M subunit) of rat creatine kinase, nor the B subunit of human and rabbit creatine kinase, suggesting that glutamine at the first position of the epitope is essential for antigen recognition by 5AH10.

L14 ANSWER 36 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:308872 HCAPLUS
DOCUMENT NUMBER: 122:78292
TITLE: Prolines and Amyloidogenicity in Fragments of the Alzheimer's Peptide .beta./A4
AUTHOR(S): Wood, Stephen J.; Wetzel, Ronald; Martin, John D.; Hurle, Mark R.
CORPORATE SOURCE: Macromolecular Sciences Department, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SOURCE: Biochemistry (1995), 34(3), 724-30
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although it is well accepted that the structure of ***amyloid*** fibrils is dominated by some form of antiparallel .beta.-sheet, there are few details on the secondary structural arrangements of the constituent peptides and how these peptides pack together in the fibril. The authors describe here the use of scanning proline mutagenesis to map the secondary structural roles of each residue in amyloidogenic peptide fragments of the Alzheimer's ***amyloid*** peptide .beta./A4. In two series of fragments related to residues 15-23 and 12-26 of .beta./A4, Pro replacement of any residue in the amyloidogenic sequence LVFFAED, corresponding to residues 17-23, leads to essentially complete loss of fibril formation and to excellent peptide soly. Since peptidyl-prolyl bonds are incapable of forming std. extended chain conformations, the results suggest that residues 17-23 make up the .beta.-sheet core of the

fibrils formed by these fragments. In contrast to the proline replacements, alanine substitutions at residues 17, 18, and 20 have no effect on fibril formation, while replacement of Phe19 reduces fibril formation to 15% of the level found for the wild-type sequence. Scanning proline mutagenesis should play a useful role in mapping the secondary structural features of larger amyloidogenic peptide sequences, including longer, physiol. relevant forms of .beta./A4. In addn., these results suggest explanations for some amyloidogenic effects obsd. in disease-related peptides and also suggest a possible role for aggregation-inhibiting insertion of prolines in protein evolution and protein design.

L14 ANSWER 37 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:131262 HCAPLUS
DOCUMENT NUMBER: 120:131262
TITLE: Topography of a binding site for small amnestic peptides deduced from structure-activity studies: relation to amnestic effect of ***amyloid*** .beta. protein
AUTHOR(S): Flood, James F.; Roberts, Eugene; Sherman, Mark A.; Kaplan, Bruce E.; Morley, John E.
CORPORATE SOURCE: Geriatr. Res. Educat. clin. Cent. (GRECC), St. Louis, MO, 63106, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1994), 91(1), 380-4
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Four peptides homologous to ***amyloid*** .beta. protein contg. the Val-Phe-Phe (VFF) sequence administered intracerebroventricularly after training caused amnesia for footshock active avoidance training in mice. Results with VFF and other peptides contg. VFF or portions there of were used to generate a topog. map for a hypothetical binding surface for amnestic peptides, termed Z. Effects on retention of footshock active avoidance training were rationalized in terms of fit to Z, making possible design of potential memory-modulating peptidic and nonpeptidic substances. Three peptides that neither improved nor impaired retention blocked the amnestic effects of .beta.-(12-28), a peptide homologous to ***amyloid*** .beta. protein, opening the way to development of substances that can antagonize the neurotoxic effects of ***amyloid*** .beta. protein on neural structures and thus attenuate symptoms and progression of Alzheimer disease.

L14 ANSWER 38 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:581364 HCAPLUS

DOCUMENT NUMBER: 115:181364
TITLE: Monoclonal antibodies to ***amyloid*** peptide
INVENTOR(S): Kim, Kwang S.; Wisniewski, Henryk M.; Miller, David L.; Chen, Cheng Mo James; Sapienza, Victor J.; Eqbal, Inge Grundke
PATENT ASSIGNEE(S): Research Foundation for Mental Hygiene, Inc., USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9012870	A1	19901101	WO 1990-US2002	19900413
W: AU, BG, BR, CA, DK, FI, HU, JP, KP, KR, NO, RO, SU				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
AU 9055250	A1	19901116	AU 1990-55250	19900413

PRIORITY APPLN. INFO.: US 1989-338302 19890414
WO 1990-US2002 19900413

AB Monoclonal antibodies (MAbs) specifically reactive with a peptide whose concn. level is elevated in individuals having Down's syndrome or Alzheimer's disease as compared to individuals of substantially the same age who are not so afflicted. They are produced by the hybridoma method using a peptide having a C-terminal sequence of Leu-Val-Phe-Phe-Ala-Glu-Asp-Val as immunogen. Also disclosed are hybridoma capable of producing the MAbs, reagent compns. incorporating the MAbs or specific-binding fragments thereof, and immunoassays. A quant. diagnostic Alzheimer ELISA method for synthetic cerebrovascular ***amyloid*** peptide (SCVAP) in soln. used MAb SCVAP 4G8-horseradish peroxidase conjugate. The sensitivity was 0.2-0.4 ng SCVAP/100.mu.L soln.

L14 ANSWER 39 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:427112 HCAPLUS
DOCUMENT NUMBER: 115:27112
TITLE: Amnestic effects in mice of four synthetic peptides homologous to ***amyloid*** .beta. protein from patients with Alzheimer disease
AUTHOR(S): Flood, James F.; Morley, John E.; Roberts, Eugene
CORPORATE SOURCE: VA Med. Cent., St. Louis, MO, 63106, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1991), 88(8), 3363-6
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Immediate post-training intracerebroventricular administration of a synthetic peptide homologous to .beta.-protein of brain ***amyloid*** , [Gln11].beta.-(1-28), caused amnesia for footshock active avoidance training in mice in a dose-dependent fashion. This effect was specific to memory processing since the peptide did not cause amnesia when injected 24 h after training nor did it disturb storage or retrieval of older memories. Shorter fragments of the ***amyloid*** .beta.-protein consisting of residues 12-28, 18-28, and 12-20 also were amnestic when given intracerebroventricularly, residues 12-20 being least effective. The hippocampus, a brain structure importantly involved in learning and memory, consistently shows severe pathol. changes and deposition of ***amyloid*** in patients with Alzheimer disease. Immediate post-training bilateral intrahippocampal injection of [Gln11].beta.-(1-28) produced amnesia at much lower doses than did [Gln11].beta.-(1-28) injected intracerebroventricularly. Thus these exptl. results suggest a possible direct role of ***amyloid*** .beta.-protein or fragments thereof in an aspect of the spectrum of cognitive deficit in Alzheimer disease.

L14 ANSWER 40 OF 40 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:150835 HCAPLUS
DOCUMENT NUMBER: 110:150835
TITLE: Production and characterization of monoclonal antibodies reactive to synthetic cerebrovascular ***amyloid*** peptide
AUTHOR(S): Kim, Kwang Soo; Miller, David L.; Sapienza, Victor J.; Chen, Cheng Mo J.; Bai, Chun; Grundke-Iqbal, Inge; Currie, Julia R.; Wisniewski, H. M.
CORPORATE SOURCE: New York State Inst. Basic Res. Dev. Disabil., Staten Island, NY, USA
SOURCE: Neurosci. Res. Commun. (1988), 2(3), 121-30
CODEN: NRCOEE; ISSN: 0893-6609
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Monoclonal antibodies (Mabs) specific for synthetic cerebrovascular ***amyloid*** peptide (SCVAP) corresponding to a 24 amino acid sequence of cerebrovascular ***amyloid*** protein were obtained after fusion of mouse myeloma cells, strain NSO, with spleen cells from SCVAP immunized Balb/c mouse. Anti-SCVAP Mabs tested thus far are all reactive to the SCVAP fragment contg. amino acid residues 17-24, which is a hydrophobic region. By competitive binding inhibition assay all the Mabs tested are competing with each other confirming that they all reacted to the same epitope or overlapping epitopes of the same region of SCVAP. By immunohistol., anti-SCVAP Mab selectively stained both vascular and neuritic plaque ***amyloid*** found in Alzheimer's brain tissue. By

ELISA, anti-SCVAP Mab reacted well with both purified vascular and core ***amyloid*** antigen prepns. Paired helical filaments and microtubular assocd. Tau did not react with anti-SCVAP Mab. An ELISA using anti-SCVAP Mab detected as little as 0.2 ng of SCVAP/100 .mu.L.